1: Nippon Ika Daigaku Zasshi 1995 Aug;62(4):320-8 Related Articles, Links

[Effect of anticancer drugs on invasive capacity of human small-cell lung cancer cells in vitro]

[Article in Japanese]

Morikawa T, Shibuya M, Sakai S, Kudo S.

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The effect of anticancer drugs on invasive capacity of Lu 135 human small-cell lung cancer cells was studied in vitro. the invasive capacity decreased in a dose-dependent manner when tumor cells were treated with the anticancer drugs cisplatin and etopside. The inhibition of tumor cell invasion was almost parallel with the inhibition of tumor cell growth. The anticancer drugs also suppressed tumor cell migration and the activity of the matrix-degrading protease, type IV collagenase, activity. But they did not suppress adhesion to basement membrane protein such as laminin, fibronectin, or type IV collagen. Because tumor cells express adhesion molecules on the cell surface, the effect of the anticancer drugs on the expression of one such molecule, integrin, was also studied. Lu 135 cells expressed alpha 4/beta 1 integrin on the cell surface, and the pattern of integrin expression did not change with exposure with the anticancer drugs. These data suggest that the anticancer drugs inhibit the invasive capacity by suppression of migration and type IV collagenase activity of tumor cells, and that they do not modulate adhesion to the extracellular matrix or cell surface adhesion molecules such as integrin. Furthermore, these findings indicate that anticancer drugs may be useful for anti-metastatic therapy in patients with small-cell lung cancer.

PMID: 7559920 [PubMed - indexed for MEDLINE]

Erratum in:
- Clin Pharmacokinet 1997 Apr;32(4):323

Clinical pharmacokinetics of vinorelbine.

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Vinorelbine (5'-noranhydrovinblastine) is a recently developed semisynthetic anticancer drug which belongs to the Catharanthus alkaloid family. Its mechanism of action is only partially known but it is assumed that it acts, like vinblastine and vincristine, as an antimicrotubule agent arresting cell division in mitosis. Clinically, vinorelbine has mainly shown activity in the treatment of advanced non-small-cell lung cancer and the treatment of metastatic breast cancer. Early pharmacokinetic data were obtained with radioactive assays (radio-immunoassay or 3H-labelled vinorelbine), then with more selective high performance liquid chromatographic techniques. Vinorelbine is usually administered intravenously but there has also been some experimentation with an oral formulation. The bioavailability of a liquid filled gelatin capsule ranges between 12 and 59% with a mean value of 27% [standard deviation (SD) 12%]. Vinorelbine is rapidly absorbed with peak serum concentration reached within 2 hours. In vitro, vinorelbine is mainly distributed into the blood cells, especially platelets (78%) and lymphocytes (4.8%) The unbound blood fraction is around 2%. In lung tissue vinorelbine concentrations are much higher than in serum, by up to 300-fold 3 hours after administration. Little is known about the biotransformation of vinorelbine. Desacetylvinorelbine is considered to be a minor metabolite and is only found in urine fractions, representing 0.25% of the injected dose. Urinary excretion of vinorelbine is low, accounting for less than 20% of the dose. Faecal elimination has been demonstrated in 2 patients who were administered 3H-labelled vinorelbine; the amount of radioactivity recovered in the faeces was 33.9 and 58.4% for the 2 patients, respectively. The pharmacokinetic profile of vinorelbine is often described as a 3-compartment model characterised by a long terminal half-life (t1/2) that varies between 20 and 40 hours and a large apparent volume of distribution (Vd) of around 70 L/kg. Systemic clearance ranges between 72.54 and 89.46 L/h (1209 and 1491 ml/min) when determined by high performance liquid chromatography and is higher than that reported by radioimmunoassay [46.2 L/h (770 ml/min)]. This could be due to the greater specificity of the chromatographic method. Vinorelbine has been administered by continuous intravenous infusion over 4 days. Steady-state was reached and the concentrations obtained were above the in vitro IC50 (concentration of drug causing 50% inhibition). The effect of liver disease on vinorelbine pharmacokinetics has

1: Clin Exp Metastasis 1997 Jul;15(4):361-7 Related Articles, Links

Effect of cisplatin and BCNU on MMP-2 levels in human glioblastoma cell lines in vitro.

Chintala SK, Ali-Osman F, Mohanam S, Rayford A, Go Y, Gokaslan ZL, Gagercas E, Venkaiah B, Sawaya R, Nicolson GL, Rao JS.

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Matrix metalloproteinases (MMPs) play an important role in various physiological and pathological conditions such as tissue remodeling, and cancer cell invasion and metastasis. The aim of this study was to determine the effect of the antitumor compounds cis-dichlorodiammine platinum (ii) (cisplatin) and 1, 3 bis (2-chloroethyl)-1-nitrosourea (BCNU) on 72-kDa type IV collagenase activity (MMP-2) in human gliomas. Human glioblastoma cell lines were treated with cisplatin (25 microM), and BCNU (50 microM), and the levels of MMP-2 were estimated in serum-free conditioned medium and in cell extracts at different time intervals. Gelatin zymography revealed increased levels of MMP-2 in serum-free conditioned medium and in cell extracts of untreated glioblastoma cell cultures during a 72-h period. In contrast, MMP-2 levels were significantly decreased in cisplatin-treated cells both in conditioned medium and cell extracts. However, no significant changes of MMP-2 levels were noted in BCNU-treated cells. Quantitative analysis of MMP-2 enzyme activity by densitometry and amount of MMP-2 protein by ELISA showed significantly decreased levels of MMP-2 in cisplatin-treated cells compared to BCNU and untreated glioblastoma cells. The results indicate that decreased levels of MMP-2 might represent an additional mechanism by which cisplatin provides its antineoplastic effects.

PMID: 9219724 [PubMed - indexed for MEDLINE]

1: Br J Surg 1995 Sep;82(9):1192-6 Related Articles, Links

In vitro regulation of human breast cancer cell adhesion and invasion via integrin receptors to the extracellular matrix.

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Department of Surgery, St Bartholomew's Hospital, UK.

The extracellular matrix consists of the interstitium and the basement membrane. Cellular interaction with fibronectin, laminin and collagen provides a possible mechanism by which cancer cells adhere, invade and metastasize. The integrins are a major family of adhesion molecules that recognize epitopes on the extracellular matrix as ligands. These include the alpha 2 beta 1, alpha 3 beta 1, alpha v beta 1 and alpha v beta 5 integrins, most of which were found to be expressed on MCF-7, T47D, MDA-MB-231, ZR75-1 and Hs578T breast cancer cell lines. Each cell line adhered to the matrix proteins in a dose-dependent manner and was inhibited by monoclonal antibodies against relevant integrins. Only Hs578T was significantly invasive through fibronectin but both Hs578T and MDA-MB-231 invaded through laminin and type IV collagen in an in vitro assay. The invasive potential of these cell lines could be inhibited by integrin antibodies added to cells before incubation, but the addition of antibodies after cells were allowed to adhere to the matrix failed to inhibit invasion. Inhibition of cellular adhesion to the matrix reduced the invasive potential of breast cancer cell lines. As integrin antibodies inhibit cell invasion in vitro, the integrins may be of potential value as antitumour therapeutic agents.

PMID: 7551993 [PubMed - indexed for MEDLINE]

1: Cancer Lett 1996 Jun 5;103(2):201-8 Related Articles, Links

ELSEVIER SCIENCE FULL-TEXT ARTICLE

Modulation of matrix metalloprotease-2 and invasion in human glioma cells by alpha 3 beta 1 integrin.

Chintala SK, Sawaya R, Gokaslan ZL, Rao JS.

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We have investigated the effect of integrin antibodies to a well-characterized alpha 5 beta 1 (fibronectin receptor) and to a multi-specific alpha 3 beta 1 (laminin, collagen, and fibronectin receptor), on the expression of matrix metalloproteases and the invasion ability of two human glioblastoma cell lines, SNB19 and U251. Cell adhesion assays indicated that both cell lines adhere to fibronectin, type IV collagen and laminin. Adhesion of cells to fibronectin was inhibited by a RGD peptide. Cells treated with anti-alpha 3 beta 1 or anti-alpha 5 beta 1 antibodies expressed increased levels of MMP-2. An in vitro matrigel assay also showed that the alpha 3 beta 1 antibody-treated cells had greater invasive ability than the controls. Immunofluorescence data showed that glioma cells treated with either anti-alpha 3 beta 1 or anti-alpha 5 beta 1 antibodies expressed diminished alpha 3 beta-1 and alpha 5 beta 1 integrins relative to the controls. The data show that treatment of cells with alpha 3 beta 1 antibody diminishes the integrin expression on the cell surface and increases the MMP-2 activity and invasiveness.

PMID: 8635158 [PubMed - indexed for MEDLINE]

1: Cancer Res 1993 Jul 15;53(14):3411-5 Related Articles, Links

The 72 kDa type IV collagenase is modulated via differential expression of alpha v beta 3 and alpha 5 beta 1 integrins during human melanoma cell invasion.

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Department of Ophthalmology, University of Arizona, Tucson 85724.

We have recently reported that concomitant with an increase in invasiveness, there is an increase in the expression and secretion of the matrix-degrading 72 kDa gelatinase A/type IV collagenase (MMP-2) in a moderately invasive human melanoma cell line (A375M) upon perturbation of the alpha v beta 3 classic vitronectin receptor. In the present study, we have extended these observations to include a highly invasive and metastatic melanoma cell line (C8161) which expresses a comparable amount of the alpha 5 beta 1 integrin (classic fibronectin receptor), but very little alpha v beta 3 integrin on its surface. When perturbed with an anti-alpha 5 beta 1 antibody, C8161 cells are 89% more invasive in vitro, and express and secrete increased levels of the gelatinase A. These changes were not elicited using antibodies to the alpha v beta 3 integrin. In addition, a 73% increase in invasion of C8161 cells through a fibronectin-enhanced matrix occurred, which could be abrogated by neutralizing antibodies to gelatinase A. Furthermore, we attempted to transiently mimic the invasive phenotype of the C8161 cells by diminishing the alpha v beta 3 integrin from the A375M cell surface through fluorescence-activated cell sorting selection or deoxynojirimycin treatment, and found these cells to be 30-50% more invasive than the parental population. These data suggest that alternative modulation and signaling events could be involved in melanoma tumor cell invasion as a result of the differential expression of integrins, and strictly cataloging the presence of these integrins is but an initial step in the analysis of their functional activity.

PMID: 7686818 [PubMed - indexed for MEDLINE]

☐ 1: J Cell Biol 2001 Apr 30;153(3):491-501 Related Articles, Links

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An RGD sequence in the P2Y(2) receptor interacts with alpha(V)beta (3) integrins and is required for G(o)-mediated signal transduction.

Erb L, Liu J, Ockerhausen J, Kong Q, Garrad RC, Griffin K, Neal C, Krugh B, Santiago-Perez LI, Gonzalez FA, Gresham HD, Turner JT, Weisman GA.

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The P2Y(2) nucleotide receptor (P2Y(2)R) contains the integrin-binding domain arginine-glycine-aspartic acid (RGD) in its first extracellular loop, raising the possibility that this G protein-coupled receptor interacts directly with an integrin. Binding of a peptide corresponding to the first extracellular loop of the P2Y(2)R to K562 erythroleukemia cells was inhibited by antibodies against alpha(V)beta (3)/beta(5) integrins and the integrin-associated thrombospondin receptor, CD47. Immunofluorescence of cells transfected with epitope-tagged P2Y(2)Rs indicated that alpha(V) integrins colocalized 10-fold better with the wild-type P2Y(2)R than with a mutant P2Y(2)R in which the RGD sequence was replaced with RGE. Compared with the wild-type P2Y(2)R, the RGE mutant required 1,000-fold higher agonist concentrations to phosphorylate focal adhesion kinase, activate extracellular signal-regulated kinases, and initiate the PLC-dependent mobilization of intracellular Ca(2+). Furthermore, an anti-alpha(V) integrin antibody partially inhibited these signaling events mediated by the wild-type P2Y(2)R. Pertussis toxin, an inhibitor of G(i/o) proteins, partially inhibited Ca(2+) mobilization mediated by the wild-type P2Y(2)R, but not by the RGE mutant, suggesting that the RGD sequence is required for P2Y(2)R-mediated activation of G(o), but not G(q). Since CD47 has been shown to associate directly with G(i/o) family proteins, these results suggest that interactions between P2Y(2)Rs, integrins, and CD47 may be important for coupling the P2Y(2)R to G(o).

PMID: 11331301 [PubMed - indexed for MEDLINE]

1: J Biol Chem 2001 Nov 9;276(45):42172-81

Related Articles, Links

Molecular cloning of POEM: a novel adhesion molecule that interacts with alpha8beta1 integrin.

Morimura N, Tezuka Y, Watanabe N, Yasuda M, Miyatani S, Hozumi N, Tezuka Ki K.

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Cell adhesion molecules are involved in a number of biological functions, such as cell survival, cell differentiation, tissue repair, and development. A novel molecule, POEM (preosteoblast epidermal growth factor-like repeat protein with meprin, A5 protein, and receptor protein-tyrosine phosphatase mu domain), was isolated by reverse transcription-polymerase chain reaction using a set of degenerate primers designed after other known epidermal growth factor (EGF)-like motifs. From its structure, POEM was suggested to be a novel adhesion molecule with five EGF-like domains, an Arg-Gly-Asp (RGD) cell binding motif, and a meprin, A5 protein, and receptor protein-tyrosine phosphatase mu (MAM) domain. By in situ hybridization using embryonic day 16.5 (E16.5) mouse embryos, strong expression of POEM mRNA was observed in developing kidney renal tubules, parathyroid and thyroid glands, developing bone, tooth germ, and endocrine organs of the brain. The inner ear, skeletal muscle, smooth muscle (except for the vascular system), and skin were also positive for POEM expression. Bacterial recombinant POEM protein containing the RGD sequence and MAM domain showed strong cell adhesion, spreading, and survival-promoting activities. By mutating the RGD sequence to RGE, the cell spreading and survival activities were significantly decreased, but the MAM domain was shown to contribute only to cell adhesion and not to cell spreading and survival-promoting activities. The distribution of POEM in several tissues was close to that of alpha(8)beta(1) integrin. Therefore, we conducted cell adhesion assays using KA8 cells, a K562 leukemia clone stably expressing alpha(8) integrin. Parental K562 cells, which expressed alpha(5)beta(1) integrin, bound to fibronectin but not to POEM. On the other hand, KA8 cells showed strong binding and spreading on both fibronectin and POEM. These results suggest that POEM is a novel ligand for alpha(8)beta(1) integrin and that POEM may be involved in the development and function of various tissues, such as kidney, bone, muscles, and endocrine organs.

PMID: 11546798 [PubMed - indexed for MEDLINE]

1: Bioessays 1990 Dec;12(12):583-90 Related Articles, Links

Integrins and tumor invasion.

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Cell-extracellular matrix interactions are important in the process of tumor cell invasion and metastasis. In particular, the interactions of tumor cells with basement membranes of tissue epithelial, as well as vascular endothelial, cells are likely to represent key steps in the metastatic process. The interactions between cells and the connective tissue matrix are mediated by a large family of cell surface receptors, the integrins, which represent multiple receptors for extracellular matrix and basement membrane components. Here, I review recent progress in elucidating the roles of integrins in tumor cell invasion. Altered expression of this large family of receptors on invasive tumor cells, as compared with non-invasive cells, may represent a fundamental step in the progressive expression of the invasive phenotype.

Publication Types:
- Review
- Review, Tutorial

PMID: 2080913 [PubMed - indexed for MEDLINE]

1: Clin Exp Metastasis 1992 Mar;10(2):111-20 Related Articles, Links

Integrin expression in human melanoma cells with differing invasive and metastatic properties.

Gehlsen KR, Davis GE, Sriramarao P.

La Jolla Institute for Experimental Medicine, CA.

During the process of tumor cell invasion and metastasis, tumor cells are known to interact with extracellular matrix proteins, endothelial cells, platelets and other organ-specific structures. Integrins are cell surface molecules which mediate cell-matrix and cell-cell interactions and are likely to be important for tumor cell survival and dissemination. The purpose of this study was to characterize the integrin and proteolytic enzyme repertoire from low (A375P), medium (A375M) and high metastatic (A375SM) human melanoma cell lines. These cell lines are also invasive through human amniotic membranes in vitro and their invasiveness parallels the reported metastatic phenotype. The types and levels of expression of the various integrin receptors were analysed by quantitative immunoprecipitation using a panel of monoclonal antibodies directed to known integrin subunits. In addition, cDNA probes to the integrin subunits were used in quantitative northern blot analysis. These data show that the integrin alpha v beta 3 increases 50- to 100-fold as these cells progress to a more metastatic phenotype. alpha 4 beta 1 levels also appeared to increase several fold, while other beta 1 integrins did not differ in their expression levels. The increased alpha v beta 3 expression in the more metastatic cells resulted in an increased adhesion to vitronectin and fibrinogen substrates in cell attachment assays. However, alpha v- and beta 3-specific antibodies did not inhibit A375 cell invasion through the amnion. Each cell line was found to release similar quantities of a 72-kDa gelatinase/type IV collagenase and tissue type plasminogen activator. These results suggest that during the progression of these tumor cells from a low to high metastatic phenotype, marked changes in integrin expression occurred which may facilitate interactions with platelets, endothelial cells and specific extracellular matrix proteins to promote metastasis.

PMID: 1311225 [PubMed - indexed for MEDLINE]

1: Cancer Res 1994 Apr 15;54(8):2102-7 Related Articles, Links

A monoclonal antibody inhibits adhesion to fibronectin and vitronectin of a colon carcinoma cell line and recognizes the integrins alpha v beta 3, alpha v beta 5, and alpha v beta 6.

Lehmann M, Rabenandrasana C, Tamura R, Lissitzky JC, Quaranta V, Pichon J, Marvaldi J.

Institut de Chimie Biologique, ER CNRS 079, Universite d'Aix-Marseille, France.

Using whole viable human colon carcinoma HT29 cells as immunogen, we produced a monoclonal antibody (mAb) termed 69-6-5. The antibody was functionally selected on its anti-cell-spreading activity. By immunoprecipitation of surface radiolabeled cell lysates from HT29-D4 cells (an HT29 cell clone), mAb 69-6-5 recognized a molecular complex resembling integrin heterodimers. Sequential immunodepletions with mAb to the integrin alpha v subunit demonstrated that this complex was composed of alpha v-containing integrins. Accordingly, mAb 69-6-5 reacted with integrin alpha v beta 3 immunopurified from melanoma cells and integrins alpha v beta 5 and alpha v beta 6 immunopurified from pancreatic carcinoma cells. In cell adhesion assays, the 69-6-5 mAb was able to inhibit strongly in a dose-dependent manner arginine-glycine-aspartic acid-mediated adhesion of HT29-D4 cells to vitronectin, fibronectin, or ProNectin F but not to laminin or collagen. Immunoprecipitations with beta chain-specific antisera indicated that these cells express integrins alpha v beta 5 (receptor for vitronectin) and alpha v beta 6 (receptor for fibronectin) but neither alpha v beta 1 nor alpha v beta 3. In summary, these results indicated that mAb 69-6-5 reacts with several alpha v integrins and that it can effectively interfere with the adhesive functions of at least alpha v beta 5 and alpha v beta 6, which represent the major receptors on HT29-D4 cells responsible for their adhesion on vitronectin and fibronectin.

PMID: 7513610 [PubMed - indexed for MEDLINE]

Inhibitory effects of adhesion oligopeptides on the invasion of squamous carcinoma cells with special reference to implication of alpha v integrins.

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We studied invasion-related adhesion events in vitro using three squamous carcinoma cell lines (HSC-3), poorly differentiated type; OSC-19, well-differentiated type; and KB cells, undifferentiated type). An in vitro invasion assay through matrigel in the transwell chamber revealed that HSC-3 cells were most invasive, OSC-19 cells moderately invasive and KB cells least invasive. Inhibition assay of invasion using synthetic peptides RGD, RGDV, RGDS, RGDT, IKVAV and YIGSR, showed that invasion of the three cell lines was significantly inhibited by RGDV. There were other peptides that inhibited invasion significantly including IKVAV for HSC-3, and RGDS and YIGSR for OSC-19. HSC-3 cells and OSC-19 cells adhered to fibronectin, laminin, vitronectin, and type IV collagen, and KB cells did not adhere to laminin but did to fibronectin, vitronectin and collagen type IV. Pretreatment of cells with RGDV peptide in the attachment assay reduced the ability of these cells to bind to vitronectin and fibronectin more efficiently than pretreatment with RGDS. Anti-alpha v antibodies inhibited adhesion of HSC-3, OSC-19 and KB cells to vitronectin, but anti-beta 1 antibodies did not inhibit adhesion. Immunofluorescent microscopic examinations showed that all cell lines were positive for anti-beta 5 and anti-alpha v antibodies, and only HSC-3 cells were positive for anti-beta 3 antibody. alpha 5 beta 1 was not clearly demonstrated in any of the cell lines. RGDV was the most effective inhibitor of squamous cell carcinoma invasion among the synthetic oligopeptides used in this experiment, and it is suggested that it affects alpha v beta 3- and/or alpha v beta 5-mediated carcinoma cell invasion.

PMID: 7536195 [PubMed - indexed for MEDLINE]

☐ 1: Neoplasia 2002 May-Jun;4(3):191-4 Related Articles, Links

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The role of alpha(v)beta(3) in prostate cancer progression.

Cooper CR, Chay CH, Pienta KJ.

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Integrin alpha(v)beta(3) is involved in varied cell biological activities, including angiogenesis, cell adhesion, and migration on several extracellular matrix components. Although alpha(v)beta(3) is not typically expressed in epithelial cells, it is expressed in macrophages, activated leukocytes, cytokine-stimulated endothelial cells, osteoclasts, and certain invasive tumors. Interestingly, the adhesion and migration of breast cancer cells on bone matrix are mediated, in part, by alpha(v) beta(3). Similar to breast cancer cells, prostate cancer cells preferentially metastasize to the bone. The biological events that mediate this metastatic pattern of prostate cancer are not well defined. This review discusses the role alpha(v)beta(3) plays in prostate cancer progression, with specific emphasis on bone metastasis and on alpha(v) beta(3) signaling in prostate cancer cells. The data suggest that alpha(v) beta(3), in part, facilitates prostate cancer metastasis to bone by mediating prostate cancer cell adhesion to and migration on osteopontin and vitronectin, which are common proteins in the bone microenvironment. These biological events require the activation of focal adhesion kinase and the subsequent activation of PI-3 kinase/Akt signaling pathway.

Publication Types:
- Review

Review, Tutorial

PMID: 11988838 [PubMed - indexed for MEDLINE]

1: Int J Biochem Cell Biol 1997 May;29(5):721-5 Related Articles, Links

ELSEVIER SCIENCE FULL-TEXT ARTICLE

The alpha v beta 3 integrin "vitronectin receptor".

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The alpha v beta 3 "vitronectin receptor" is a member of the integrin superfamily of adhesion molecules. As such, this 160/85 kDa heterodimeric protein exhibits many of the typical structural and functional features of integrins. It mediates cell adhesion to extracellular matrix by recognizing the conserved arg-gly-asp (RGD) sequence of several plasma and matrix proteins. Recently, it has also been shown that alpha v beta 3 is involved in signal transduction and cell to cell interactions. alpha v beta 3 is highly expressed in bone resorbing cells, osteoclasts, and upregulated in response to vascular damage, during angiogenesis and in certain types of malignancy. Antagonists of alpha v beta 3 are being developed for use in a variety of diseases associated with altered receptor function or level.

Publication Types:
- Review
- Review, Tutorial

PMID: 9251239 [PubMed - indexed for MEDLINE]

1: J Biol Chem 1994 Oct 28;269(43):26926-32

Vitronectin-driven human keratinocyte locomotion is mediated by the alpha v beta 5 integrin receptor.

Kim JP, Zhang K, Chen JD, Kramer RH, Woodley DT.

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Vitronectin is a soluble serum factor that is known to promote epiboly of keratinocytes in explant cultures and enhance cell spreading and attachment to matrix. Recently, vitronectin was demonstrated to promote human keratinocyte locomotion. The mechanism(s) by which vitronectin enhances keratinocyte migration is unknown. In this study, we quantitated the vitronectin-driven migration of human keratinocytes in the presence of antibodies to vitronectin receptors. We found that vitronectin's effect of promoting human keratinocyte migration was inhibited by antibody-directed against the alpha v beta 5 receptor. In addition, we surface-labeled human keratinocytes, chromatographed extracts of the cell membranes on a vitronectin column, and then immunoprecipitated the bound and eluted proteins with antibodies to specific vitronectin receptors. We identified the vitronectin receptors on human keratinocytes as bands of 150,000 and 100,000 daltons without reduction and as 125,000 and 110,000 daltons under reducing conditions. Immunoprecipitation with specific antibodies identified the major receptor to be the alpha v beta 5 integrin. In addition, we quantitated vitronectin-driven migration of human keratinocytes in the presence of Arg-Gly-Asp (RGD) and control peptides. We found that the presence of RGD, but not control peptide, inhibited vitronectin-driven migration of human keratinocytes. These studies demonstrate that human keratinocytes express vitronectin receptors and use the alpha v beta 5 receptor for cellular locomotion.

PMID: 7523414 [PubMed - indexed for MEDLINE]

1: Nature 1996 Oct 3;383(6599):441-3 Related Articles, Links

Comment in:
- Nature. 1996 Oct 3;383(6599):390-1.

The serpin PAI-1 inhibits cell migration by blocking integrin alpha V beta 3 binding to vitronectin.

Stefansson S, Lawrence DA.

Biochemistry Department, J.H. Holland Laboratory, American Red Cross, Rockville, Maryland 20855, USA.

During wound healing, migrating cells increase expression of both the vitronectin receptor (VNR) integrins and plasminogen activators. Here we report that vitronectin significantly enhances the migration of smooth muscle cells (SMCs), and that the specific VNR alpha V beta 3 is required for cell motility. We also show that the alpha V beta 3 attachment site on vitronectin overlaps with the binding site for plasminogen activator inhibitor (PAI)-1, and that the active conformation of PAI-1 blocks SMC migration. This effect requires high-affinity binding to vitronectin, and is not dependent on the ability of PAI-1 to inhibit plasminogen activators. Formation of a complex between PAI-1 and plasminogen activators results in loss of PAI-1 affinity for vitronectin and restores cell migration. These data demonstrate a direct link between plasminogen activators and integrin-mediated cell migration, and show that PAI-1 can control cell-matrix interactions by regulating the accessibility of specific cell-attachment sites. This indicates that the localization of plasminogen activators at sites of focal contact does not initiate a proteolytic cascade leading to generalized matrix destruction, but instead is required to expose cryptic cell-attachment sites necessary for SMC migration.

PMID: 8837777 [PubMed - indexed for MEDLINE]